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Equivalence of pegfilgrastim and filgrastim in lymphoma patients treated with BEAM followed by autologous stem cell transplantation

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Abstract: Objective: To evaluate the impact of pegfilgrastim on engraftment, hospital stay and resources in patients with Hodgkin's and non-Hodgkin's lymphoma after conditioning with high-dose BEAM followed by autologous peripheral blood stem cell transplantation (APBSCT) compared with filgrastim. Methods: We reviewed patient charts and our prospective transplantation database for clinical data from the post-transplant period. An integrated cost analysis, including the use of blood products and length of hospital stay, was also performed. Results: Fourteen (26%) patients with Hodgkin's lymphoma and 40 (74%) patients with non-Hodgkin's lymphoma were analyzed. Thirty-four (68%) patients received single-dose pegfilgrastim (6 mg), and 20 (32%) patients received daily filgrastim (5 g/kg) after APBSCT. No differences were observed regarding duration of neutropenia grade 4 (pegfilgrastim median 7 days/filgrastim median 8 days; $p = 0.13$), thrombocytopenia grade 4 (7/9.5 days, respectively; $p = 0.21$), fever (4.5/2 days; $p = 0.057$), intravenous antibiotic treatment (11/10 days; $p = 0.75$) or length of hospital stay (16.5/16 days; $p = 0.27$) between the groups. The use of pegfilgrastim resulted in 12% higher treatment-related costs when compared to filgrastim, without reaching statistical significance ($p = 0.38$). Conclusion: Pegfilgrastim appears to be equivalent to filgrastim after high-dose BEAM followed by APBSCT in the treatment of lymphoma patients.

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Equivalence of Pegfilgrastim and Filgrastim in Lymphoma Patients Treated with BEAM Followed by Autologous Stem Cell Transplantation

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Key Words

Autologous peripheral blood stem cell transplantation · BEAM · Engraftment · Filgrastim · Pegfilgrastim

Abstract

Objective: To evaluate the impact of pegfilgrastim on engraftment, hospital stay and resources in patients with Hodgkin's and non-Hodgkin's lymphoma after conditioning with high-dose BEAM followed by autologous peripheral blood stem cell transplantation (APBSCT) compared with filgrastim. **Methods:** We reviewed patient charts and our prospective transplantation database for clinical data from the post-transplant period. An integrated cost analysis, including the use of blood products and length of hospital stay, was also performed. **Results:** Fourteen (26%) patients with Hodgkin's lymphoma and 40 (74%) patients with non-Hodgkin's lymphoma were analyzed. Thirty-four (68%) patients received single-dose pegfilgrastim (6 mg), and 20 (32%) patients received daily filgrastim (5 µg/kg) after APBSCT. No differences were observed regarding duration of neutropenia grade 4 (pegfilgrastim median 7 days/filgrastim median 8 days; $p = 0.13$), thrombocytopenia grade 4 (7/9.5 days, respectively; $p = 0.21$), fever (4.5/2 days; $p = 0.057$), intravenous

antibiotic treatment (11/10 days; $p = 0.75$) or length of hospital stay (16.5/16 days; $p = 0.27$) between the groups. The use of pegfilgrastim resulted in 12% higher treatment-related costs when compared to filgrastim, without reaching statistical significance ($p = 0.38$). **Conclusion:** Pegfilgrastim appears to be equivalent to filgrastim after high-dose BEAM followed by APBSCT in the treatment of lymphoma patients.

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Introduction

Autologous peripheral blood stem cell transplantation (APBSCT) is a widely performed treatment modality for patients with multiple myeloma or relapsed/refractory Hodgkin's lymphoma (HL) and aggressive non-Hodgkin's lymphoma (NHL) [1–4]. According to the European Group for Blood and Marrow Transplantation database, 6,734 autologous stem cell transplantations were per-

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formed in lymphoma patients in 2008 (1,919 for HL patients and 4,815 for NHL patients) [5]. Treatment-related mortality is less than 5% and most often due to infectious complications during the post-transplant period [6]. To reduce the time to engraftment and eventually the risk for infections, many transplantation centers have established the use of granulocyte-colony stimulating factors (G-CSF) in the APBSCT routine, although data on their clinical benefit and general recommendations are still ambiguous [7–8]. Due to their short half-life, daily injections are necessary until neutrophil recovery has been achieved.

Pegfilgrastim (Neulasta®, Amgen) is the pegylated form of the G-CSF filgrastim (Neupogen®, Amgen). This long-term formulation has the advantage over filgrastim of a single application after the myeloablative chemotherapy, thus improving patient comfort and administration safety.

Here we report on the efficacy of pegfilgrastim in comparison to filgrastim in patients with NHL or HL receiving unmodified high-dose BEAM as conditioning regimen followed by APBSCT at our Stem Cell Transplantation Center in Zürich during the last 4 years. We analyzed only lymphoma patients receiving unmodified high-dose BEAM, to avoid any possible bias based on the heterogeneity of the administered conditioning regimens [9–11]. We also placed a special emphasis on possible differences in treatment-related costs during the post-transplant period.

Patients and Methods

Patients with NHL or HL receiving high-dose BEAM as conditioning regimen followed by APBSCT during the last 4 years (2006–2009) at our center were analyzed. The study was approved by our local ethic committee.

Patients received either pegfilgrastim or daily filgrastim after APBSCT. Pegfilgrastim was administered as single fixed dose of 6 mg subcutaneously at day +1 after stem cell retransfusion. Filgrastim was given at a dose of 5 µg/kg body weight subcutaneously once daily, starting at day +5 after stem cell retransfusion, until the absolute neutrophil count (ANC) was $\geq 0.5 \times 10^9$ cells/l for at least 3 consecutive days.

The BEAM regimen consisted of carmustine 1×300 mg/m², etoposide 8×150 mg/m² b.i.d., cytarabine 8×200 mg/m² b.i.d. and melphalan 1×140 mg/m², followed by APBSCT.

Patients treated for disease entities other than NHL or HL and patients receiving a dose-reduced BEAM regimen (i.e. 'BEAM elderly') were excluded from this analysis.

The medical records of the patients and our prospective transplantation database were screened for length of hospital stay, appearance and duration of fever, use of intravenous (i.v.) antibiotics and need for red blood cell and platelet transfusions during hospital stay. These factors were compared between the groups.

Table 1. Patient characteristics

Parameter	Filgrastim use (n = 20)	Pegfilgrastim use (n = 34)	p value
Age, years			0.8
Median	51	51.7	
Range	24–67.6	18.8–66.2	
Gender, n (%)			0.39
Male	14 (70)	19 (56)	
Female	6 (30)	15 (44)	
CD34+ cells reinfused, $\times 10^6$ cells/kg b.w.			0.76
Median	5.2	5.3	
Range	2.3–12	2.1–20.1	
Entity, n (%)			0.49
Non-Hodgkin's lymphoma	13 (65)	27 (79)	
Hodgkin's lymphoma	7 (35)	7 (21)	
NHL subtype, n (%)			0.79
DLBCL	7 (54)	8 (30)	
Follicular lymphoma	1 (7.5)	4 (15)	
Mantle cell lymphoma	4 (31)	9 (33)	
Peripheral T-NHL	1 (7.5)	3 (11)	
Anaplastic large T-NHL	0	2 (7)	
Dendritic sarcoma	0	1 (4)	

CD34 = Cluster of differentiation 34; DLBCL = diffuse large B-cell lymphoma.

Neutropenia was defined as $ANC < 0.5 \times 10^9$ cells/l. Fever was defined as body temperature $\geq 38.4^\circ\text{C}$. Every day of fever was considered for analysis when a body temperature over this cut-off was documented in the patient charts. Hospitalization time was defined as time from the day of stem cell reinfusion (day 0) to the day of patient discharge.

Statistical Analyses

Statistical comparisons of patient characteristics were made using either a Mann-Whitney U test, or a Fisher's exact test, as appropriate. Continuous clinical outcomes are presented as median (range), and compared using the Mann-Whitney U test, while binary clinical outcomes are presented as percentages, and compared using Fisher's exact test. Cost analysis is based on the average cost of antibiotics and blood products, average length of stay, and average cost of filgrastim or pegfilgrastim per patient (compared with Kruskal-Wallis test).

All analyses were performed in the R programming language [12].

Results

Patient Demographics

Between January 2006 and December 2009, a total of 54 patients with NHL (n = 40; 74%) or HL (n = 14; 26%)

Table 2. Clinical outcomes in lymphoma patients treated with BEAM

Parameter	Filgrastim use (n = 20)	Pegfilgrastim use (n = 34)	p value
Length of hospital stay, days	16 (11–35)	16.5 (12–32)	0.27
Time to engraftment, days	9 (7–13)	9 (8–22)	0.55
Duration of neutropenia grade 4, days	8 (5–14)	7 (5–22)	0.13
Duration of thrombocytopenia grade 4, days	9.5 (2–19)	7 (3–20)	0.21
Duration of fever, days	2 (0–19)	4.5 (0–16)	0.057
Duration of i.v. antibiotic treatment, days	10 (0–23)	11 (4–28)	0.75
Red blood cell transfusions, n	4 (0–13)	2 (0–9)	0.27
Platelet transfusions, n	2 (1–8)	2.5 (1–8)	0.78

Data presented as median (range). p values from Mann-Whitney U test.

Table 3. Clinical outcomes (binary) in lymphoma patients treated with BEAM

Parameter	Filgrastim (n = 20)	Pegfilgrastim (n = 34)	p value
Intravenous antibiotics	18 (90)	34 (100)	0.13
Incidence of fever	16 (80)	33 (97)	0.057
Red blood cell transfusions	17 (85)	28 (82.5)	1
Platelet transfusions	20 (100)	34 (100)	1
Transfer to ICU	1 (5)	3 (9)	1

Data presented as absolute patient numbers with percentages in parentheses. p values from Fisher's exact test. ICU = Intensive care unit.

were treated with unmodified high-dose BEAM and received subsequent G-CSF support. Thirty-four (68%) patients received single-dose pegfilgrastim, and 20 (32%) patients received filgrastim after APBSCT, respectively. Filgrastim was applied after APBSCT for a median of 7.5 days (range 5–16 days). The main patient characteristics were well balanced between the 2 groups (table 1).

Efficacy

The median time to neutrophil engraftment after pegfilgrastim was identical to the engraftment achieved with filgrastim [median 9 days (range 8–22) for pegfilgrastim vs. 9 days (range 7–13) for filgrastim; $p = 0.55$], and the median duration of neutropenia grade 4 did not differ significantly between the 2 patient populations, with a median of 7 days (range 5–22) for pegfilgrastim versus 8 days (range 5–14) for filgrastim ($p = 0.13$). In addition, no difference regarding the duration of thrombo-

cytopenia grade 4 was seen between the 2 groups (median 7 days, range 3–20, for pegfilgrastim vs. 9.5 days, range 2–19, for filgrastim, $p = 0.21$). Also no significant differences were observed regarding the number of red blood cell or platelet transfusions, the duration of fever and the duration of i.v. antibiotic treatment between the 2 groups (table 2).

In the binary outcome analysis, no significant difference was noted in the number of patients needing i.v. antibiotics or blood products. In addition, there were no differences regarding the incidence of fever or the need for transfer to the intensive care unit between the 2 groups (table 3).

Cost Analysis

Cost analysis was performed using the Swiss drug prices listed for the year 2008. The median cost per patient for filgrastim was 1,950 Swiss francs (CHF), compared with CHF 2,077 for pegfilgrastim ($p = 0.16$, Mann-Whitney U test). An integrated cost analysis including the costs of G-CSF used, the infused blood products and the hospital stay showed an additional expenditure of 12% for patients receiving pegfilgrastim during the post-transplant period, without being statistically significant ($p = 0.38$, Mann-Whitney U test).

Discussion

Our study objective was to assess the impact of pegfilgrastim on the clinical outcome of patients with NHL or HL who received unmodified BEAM as conditioning regimen followed by subsequent stem cell retransfusion.

In our analysis of a homogenous patient collective we showed that administration of pegfilgrastim after high dose BEAM and APBSCT is as efficacious as filgrastim. We did not find differences regarding time to engraftment, length of hospital stay or the need for blood products and i.v. antibiotics. This finding is in accordance with studies demonstrating similar efficacy of pegfilgrastim and filgrastim in patients who received conventionally dosed myelosuppressive chemotherapy [13–14].

To our knowledge, this is the largest analysis so far focusing exclusively on patients receiving unmodified BEAM as conditioning regimen followed by APBSCT, and we were able to demonstrate that pegfilgrastim is not inferior to filgrastim. The available data so far on this topic have been achieved by analyzing heterogeneous patient cohorts treated with different conditioning regimens [15–17]. Recently, a study focused on lymphoma patients who received BEAM or BEAC (conditioning regimen with carmustine, etoposide, cytarabine and cyclophosphamide) as conditioning regimen [18]. However, high-dose chemotherapy regimens differ in terms of toxicities, and the results of the patient outcome during the post-transplant period are likely to be influenced primarily by this heterogeneity [9–11, 19].

The median cost of filgrastim needed to achieve an engraftment was lower than the cost of a single-dose of pegfilgrastim, and this additional expenditure could not

be counterbalanced by a shortening of the hospital stay or less supportive measures like i.v. antibiotics or blood products. In an integrated cost analysis we observed an additional expenditure of 12% for patients treated with pegfilgrastim, although this difference did not meet statistical significance.

To conclude, in our experience, pegfilgrastim appears to be equivalent to filgrastim after conditioning chemotherapy with high-dose BEAM followed by APBSCT. We did not see any differences regarding time to engraftment, the length of hospital stay or the need for i.v. antibiotics and blood products. Pegfilgrastim may be considered as a therapeutic option in patients treated with BEAM and APBSCT.

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Disclosure Statement

The authors report no conflicts of interest.

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